# Oral premedication for operations on the face under local anesthesia: a placebo-controlled double-blind trial

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Abstract: Modern strategies for preventing or controlling pain and anxiety demand a premedication for operations using local anesthesia and for those using sedation or general anesthesia. For optimal patient care, the premedication should be given orally and, with respect to the outpatient basis of the operations, should have a short recovery period. Midazolam, one of the most favored premedications for general anesthesia, has been recommended as a premedication for operations using local anesthesia as well. However, midazolam has only sedative-anxiolytic effects and does not reduce pain sensation, which should be mandatory for operations using local anesthesia. A further requirement is the maintenance of stable hemodynamics for the prevention of postoperative hematomas, especially in the face. For these reasons, another premedication meeting all requirements (anxiolysis, analgesia, and stable hemodynamics) was researched. A randomized, double-blind prospective study was performed from March of 1997 to June of 1998. Five groups totalling 150 patients were included in the study; each group contained 30 patients who had operations performed solely on the face. In the first four groups, the effect of midazolam (0.15 mg/kg(-1)), morphine (0.3 mg/kg(-1)), and clonidine (1.5 microg/kg(-1)) administered orally was compared with a placebo. The fifth group was the control group and received no premedication. To evaluate the effects of the premedications, a corresponding questionnaire was completed independently by the patient and surgeon. With regard to the anxiolytic or analgesic properties of the premedication, 61 percent of the patients preferred pain reduction to anxiety control, and 24 percent of patients preferred reduction of anxiety. The remainder insisted on a reduction of both properties (8 percent) or had no preference (7 percent). Reduction of anxiety was largest in the midazolam and the clonidine groups, but the difference was not significant. The least pain during the application of local anesthesia was experienced by the morphine group (37 percent) and the clonidine group (33 percent), in contrast to the midazolam group (60 percent) ($p = 0.04$). Morphine and clonidine met the requirements of pain reduction equally well. Nevertheless, considering the rate and intensity of adverse effects with respect to hemodynamic compromises, nausea, and emesis, clonidine is even better suited as an oral premedication for operations on the face using local anesthesia.

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# Oral Premedication for Operations on the Face under Local Anesthesia: A Placebo-Controlled Double-Blind Trial

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Modern strategies for preventing or controlling pain and anxiety demand a premedication for operations using local anesthesia and for those using sedation or general anesthesia. For optimal patient care, the premedication should be given orally and, with respect to the outpatient basis of the operations, should have a short recovery period. Midazolam, one of the most favored premedications for general anesthesia, has been recommended as a premedication for operations using local anesthesia as well. However, midazolam has only sedative–anxiolytic effects and does not reduce pain sensation, which should be mandatory for operations using local anesthesia. A further requirement is the maintenance of stable hemodynamics for the prevention of postoperative hematomas, especially in the face. For these reasons, another premedication meeting all requirements (anxiolysis, analgesia, and stable hemodynamics) was researched. A randomized, double-blind prospective study was performed from March of 1997 to June of 1998. Five groups totalling 150 patients were included in the study; each group contained 30 patients who had operations performed solely on the face. In the first four groups, the effect of midazolam (0.15 $mg/kg^{-1}$), morphine (0.3 $mg/kg^{-1}$), and clonidine (1.5 $\mu g/kg^{-1}$) administered orally was compared with a placebo. The fifth group was the control group and received no premedication. To evaluate the effects of the premedications, a corresponding questionnaire was completed independently by the patient and surgeon. With regard to the anxiolytic or analgesic properties of the premedication, 61 percent of the patients preferred pain reduction to anxiety control, and 24 percent of patients preferred reduction of anxiety. The remainder insisted on a reduction of both properties (8 percent) or had no preference (7 percent). Reduction of anxiety was largest in the midazolam and the clonidine groups, but the difference was not significant. The least pain during the application of local anesthesia was experienced by the morphine group (37 percent) and the clonidine group (33 percent), in contrast to the midazolam group (60 percent) ($p = 0.04$). Morphine and clonidine met the requirements of pain reduction equally well. Nevertheless, considering the rate and intensity of adverse effects with respect to hemodynamic compromises, nausea, and emesis, clonidine is even better suited as an oral premedication for operations on the face using local anesthesia. (*Plast. Reconstr. Surg.* 108: 637, 2001.)

Increasingly, plastic surgery procedures are performed in ambulatory settings with conscious or deep sedation, avoiding general anesthesia. Guidelines for such operations include recommendations for sedation and sufficient analgesia.[1]

Modern strategies for anxiety and pain prevention[2–4] require a premedication for operations using local anesthesia. In contrast to operations using general anesthesia, for which the sedative-anxiolytic properties of a premedication are sufficient, operations using local anesthesia require both anxiolytic and analgesic effects, because the application of local anesthesia is always painful. For optimal patient care, such premedication should be given orally and, because of the outpatient basis of such operations, should have a short recovery period. *Midazolam*, a benzodiazepine and one of the most often-used premedications for general anesthesia, is a purely sedative, sleep-inducing drug characterized by the rapid onset of action and a short sojourn in the body.

After oral administration of 0.1 to 0.2 $mg/kg^{-1}$, 30 to 40 minutes before the operation, midazolam is absorbed completely within 20 minutes. Besides its obvious sedative properties, it also possesses some anticonvulsive and

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muscle-relaxant effects. Midazolam has no analgesic effect; on the contrary, it seems to decrease the plasma beta-endorphin levels, lowering the pain threshold.[5–8] Midazolam is metabolized rapidly and has a half-life of 2½ hours.

The few restrictions on use include patients with severe psychosis or those of very advanced age. Undesirable effects are rare inasmuch as midazolam has a broad therapeutic margin. No serious interactions with other medications have been observed.

*Morphine*, a pure morphine sulfate-pentahydrate, is well known for its potent analgesic effect. Orally administered (0.3 mg/kg$^{-1}$), it is absorbed quickly and should be given at least 30 minutes before surgery. Morphine is metabolized completely and its half-life is 3 hours. Recovery time after surgery is usually quick, but there are a few serious and frequent adverse effects (e.g., dose-dependent respiratory depression, nausea, and vomiting).

*Clonidine* is a centrally acting $\alpha_2$-adrenoceptor partial agonist. Clonidine had been used for years as an anti-hypertonic agent. Besides its influence on heart rate, cardiac output, and systemic blood pressure, it has interesting effects on consciousness and pain transmission. There is convincing evidence that clonidine leads to evident sedation, anxiolysis, central anesthesia, and reduced pain sensitivity at peripheral nerve endings.[9–17] The appropriate dose for premedication is 1.5 $\mu$g/kg$^{-1}$ administered orally. The peak serum concentration occurs in 60 to 90 minutes. Clonidine's half-life is 8 to 12 hours. Despite this relatively long sojourn in the body, clonidine-induced sedation is not noticeable postoperatively, and recovery time is negligible. Adverse effects on blood pressure, heart rate, and rhythm are dose-dependent and are usually not evident with the recommended dose for oral premedication.

The objectives of this study were to compare midazolam, morphine, and clonidine with respect to the extent of sedation, anxiolysis, and analgesia, along with the incidence and severity of respiratory and cardiovascular compromises or nausea and emesis.

## Patients and Methods

From March of 1997 to June of 1998 a double-blind prospective trial was performed. A total of 150 male and female patients were randomly divided into five groups, with each group containing 30 patients.

The perioperative regime followed standardized conditions. Forty minutes before the onset of the operation, an oral premedication was blindly administered. Each of the first four groups received midazolam 7.5 mg, morphine 20 mg, clonidine 0.15 mg, or a placebo; all tablets were uniformly white. The fifth group acted as a control group.

Excluded from the study were patients younger than 13 and older than 92 years of age, patients with manifest cardiovascular and respiratory compromise, and patients having disorders with contraindications for sedative agents or morphine.

The operations were performed by two surgeons, and only tumor excisions (basal cell carcinoma, squamous cell carcinoma, melanoma) on the face and hair-bearing parts of the skull were included in the study. The defect closure had to be more than a primary wound closure, mostly local or regional flaps were to be used, and the operation was to last at least 1 hour.

For all operations, local anesthesia (lidocaine 1% with adrenaline 1:200 000, Gebro Pharma, GmbH, Fieberbrunn, Austria) was used, and mini-drains were applied to prevent postoperative hematoma.

Hemodynamic variables, such as blood pressure and heart rate, were measured before administration of the oral premedication, at the beginning of the operation, twice during the operation, and at the end of the operation. Oxygen saturation was measured intraoperatively. Blood pressure was measured manually; a normal systolic blood pressure level was defined as $>$90 mmHg and $<$140 mmHg. A normal heart rate was $\geq$50 and $\leq$90 beats per minute.

Each patient was monitored intraoperatively, with recording of heart rate and oxygen saturation performed automatically with a pulse oxymeter (Datex, SatLite+, Helsinki, Finland). The device alarms were set for a heart rate $<$50 and $>$90 beats per minute and for an oxygen saturation level $<$92 percent.

All procedures were conducted in the operating facilities of the hospital with complete back-up available. In the event of cardiovascular compromise or respiratory complications, an anesthesiologist with all the necessary equipment was immediately available. For ventilatory depression and hypoxemia, an oxygen

delivery supply with a nose cannula was always at our disposal.

Prolonged hypotension was treated with the intravenous administration of fluid; hypertension was counteracted with Buconif-Spray 5 mg (Sublingual Spray, Nycomed Heilwerke, Vienna, Austria), 1 to 2 pistons administered sublingually. Tachycardia was treated symptomatically, and bradycardia with atropine 0.5 to 1.0 mg intravenously. Patients with emesis were supplied with oral antiemetic agents such as metoclopramide (0.15 mg/kg$^{-1}$) (Solvay Pharmaceuticals, Brussels, Belgium).

Before discharge, the patient and surgeon independently filled in a questionnaire with corresponding questions. The patients were asked if they would have preferred a premedication with anxiolytic or analgesic properties, about their level of anxiety before the operation, and about the amount of pain during the application of the local anesthesia. In addition, they were asked about their level of satisfaction and the point at which they felt able to leave the hospital. Same-day discharge after a minimum of 4 hours was offered.

The surgeons rated their impressions on the same questions about anxiety and pain and the patient's satisfaction. The questionnaires were judged by two surgeons, one of whom was not involved with the operation itself.

*Data Analysis*

All data were listed in Microsoft Excel 97 and were analyzed using StatView 4.5 (Abacus Concepts, Berkeley, Calif.) and the Statistical Package for the Social Sciences 6.1 (Statistical Products and Service Solutions, Chicago, Ill.). Intergroup comparison on nominal variables was performed with the chi-square test and Fisher's exact test, as appropriate. Continuous variables were listed as mean ± standard deviation. Intergroup comparison of continuous variables was performed with the Kruskal-Wallis test and posthoc comparisons with the Mann-Whitney test, including the Bonferroni correction. Surgeons' and patients' questionnaires were compared using the McNemar test. For special queries the Spearman rank correlation was used; $p$ values $\leq 0.05$ were considered significant.

## RESULTS

From the 150 randomly selected patients, 71 (47 percent) were male and 79 (53 percent) were female; the distribution between genders was not significantly different ($p = 0.47$). Their ages ranged from 13 to 92 years, with a mean age of 62 years; the distribution among ages was not significantly different ($p = 0.08$). The demographic data are listed in Table I.

With regard to the patients' preference for anxiolytic or analgesic premedication, 91 patients (61 percent) preferred an analgesic premedication, 36 (24 percent) preferred an anxiolytic premedication, 12 (8 percent) preferred both anxiolytic and analgesic properties, and 11 (7 percent) expressed no preference.

The level of anxiety before the operation was comparable in all five groups (Fisher's exact $p$ value, 0.76). About half of the patients reported being anxious; the other half said they were not. The amount of anxiety was rated little, moderate, and much. Very few patients reported feeling much anxiety; most were in the placebo group (not significant) (Table II).

With regard to the extent and intensity of pain during the application of local anesthesia, the midazolam group reported experiencing the most pain (60 percent), even more so than the control group (43 percent). The placebo group reported less pain (40 percent), followed by the morphine group (37 percent), with the least pain felt by the clonidine group (33 percent). The amount of pain was rated little, moderate, and much, with reference to the visual analogue scale. The clonidine group was the only group in which nobody reported

TABLE I
Demographic Data of the 150 Patients

| | Midazolam | Morphine | Clonidine | Placebo | Control | Total | $p$ |
|---|---|---|---|---|---|---|---|
| $n$ | 30 | 30 | 30 | 30 | 30 | 150 | |
| Sex | | | | | | | |
| Male ($n$/%) | 15/50 | 12/40 | 11/37 | 16/53 | 17/53 | 71/47 | 0.47 |
| Female ($n$/%) | 15/50 | 18/60 | 19/63 | 14/47 | 13/47 | 79/53 | |
| Age | | | | | | | |
| Mean ± SD | 65.0 ± 17.4 | 67.3 ± 16.5 | 59.1 ± 17.3 | 57.0 ± 18.7 | 62.5 ± 16.2 | 62.1 ± 17.4 | 0.08 |
| Range | 20–92 | 26–90 | 19–84 | 14–86 | 13–87 | 13–92 | |

TABLE II
Patient Questionnaire: Extent of Anxiety Preoperatively

| Fear Preoperatively | Midazolam | Morphine | Clonidine | Placebo | Control | Total | *p* |
|---|---|---|---|---|---|---|---|
| Yes (*n*/%) | 16/53 | 15/50 | 12/40 | 15/50 | 12/40 | 70/47 | 0.76 |
| Little | 7 | 9 | 6 | 9 | 8 | 39 | |
| Moderate | 7 | 5 | 5 | 1 | 3 | 21 | |
| Much | 2 | 1 | 1 | 5 | 1 | 10 | |

much pain. The difference between the midazolam and clonidine groups was significant (Fisher's exact *p* value without Bonferroni correction, 0.04); differences between the other groups were not statistically significant. Table III shows the pain scale in detail.

Regarding the hemodynamic parameters, most patients showed some degree of intraoperative blood pressure variation, typically reflecting the level of anxiety or discomfort. The difference between the preoperative and intraoperative blood pressure levels among the groups was not significant, probably because of the inadequate number of patients for comparison of blood pressure (a parameter influenced by many variables). Nevertheless, when comparing the three different premedications, the clonidine group showed a clear trend toward the least increase in systolic blood pressure before, during, and especially after the operation, which is the most beneficial for the prevention of hematomas. When comparing blood pressure levels postoperatively with the control group, the clonidine group had significantly lower rates ($p = 0.0016$).

Altogether, six patients suffered from preexisting hypertension, but another six unrelated patients experienced an increase in arterial blood pressure from normal to ≥200 mmHg and needed Buconif-Spray sublingually. Two were in the midazolam group, two were in the placebo group, one was in the morphine group, and one was in the clonidine group. On the other hand, the systolic blood pressure level did not fall below 100 mmHg solely with clonidine.

Pulse rates also showed some variation at the beginning of the operations. When the pulse rate changed it was nearly always too high, but only for a short period, and no medication was necessary for this. As expected, oxygen saturation decreased beyond the 92 percent limit most often in the midazolam group (37 percent), followed by the morphine group (20 percent). In the clonidine group only three of 30 (10 percent) patients needed oxygen.

Probably because of the application of minidrains, only one patient (with hypertension) developed a postoperative hematoma, which did not require surgical intervention. Twenty-three percent of the patients experienced some degree of nausea; most from the placebo group, followed by the morphine group, and none from the midazolam and clonidine groups. Emesis occurred four times, and only in the morphine group.

Of the 120 patients who received an oral premedication, only 42 (35 percent) reported feeling able to leave the hospital immediately after the operation; 78 (65 percent) did not. Of these 78 patients, eight wanted to leave the hospital within 2 to 4 hours after the operation, eight after 4 to 8 hours, 11 after 8 to 12 hours, 34 after 24 hours, and the remaining 17 patients did not respond to this question. There were no differences between the envisaged time points of discharge for those who received premedication, but the Spearman rank correlation showed a highly significant correlation ($p = 0.0005$) between the time of a patient's discharge and age. The older the patients were, the longer they wanted to stay in the hospital; however, modern medical standards tend to overrule this desire.

TABLE III
Patient Questionnaire: Extent and Intensity of Pain during Application of Local Anesthesia

| Pain during Application | Midazolam | Morphine | Clonidine | Placebo | Control | Total | *p* |
|---|---|---|---|---|---|---|---|
| Yes (*n*/%) | 18/60 | 11/37 | 10/33 | 12/40 | 13/43 | 64/43 | 0.26 |
| Little | 10 | 5 | 8 | 6 | 9 | 38 | |
| Moderate | 6 | 5 | 2 | 5 | 3 | 21 | |
| Much | 2 | 1 | – | 1 | 1 | 5 | |

The comparison of the questionnaires between surgeons and patients revealed that the surgeons rated the level of pain higher and the level of anxiety and satisfaction lower than did the patients (differences significant).

Finally, a majority of the 104 patients (87 percent) said they would choose the combination of oral premedication and local anesthesia again and that they were satisfied with this regimen. Sixteen (13 percent) found an oral premedication to be unnecessary.

## Discussion

Operations on the face performed under local anesthesia have some peculiarities. It is well known that patients undergoing any surgical procedure on the head and neck region are exceptionally prone to postoperative hypertension. Stable (low) blood pressure during facial procedures intraoperatively and postoperatively contributes to a blood-free surgical field and prevents postoperative bleeding and hematomas.[18,19]

Besides the control of anxiety and pain as an adjunct to oral premedication, hemodynamic responses to pain should be reduced to a minimum. In our study, clonidine showed the clearest trend toward stabilizing blood pressure intraoperatively (and, above all, postoperatively), which is of major importance in preventing hematomas. On the other hand, in accordance with the literature, clonidine administered for premedication does not tend to lower blood pressure extensively.

From the three compared agents (midazolam, morphine, and clonidine), the missing first-pass effect (12 to 25 percent) and long bioavailability of clonidine attributes to stable hemodynamic parameters and to a reduced need for analgesia in the postoperative period. Adequate pain relief is essential after ambulatory surgery and is especially important in the early recovery process.[20–24]

Because of the beneficial effects of clonidine, there is considerable experience with its use as a premedication for operations performed under general anesthesia in children[25–27] and adults.[28,29] With the recommended dose for premedication (1.5 $\mu g/kg^{-1}$), Tauberger et al.[30] found no increase in hypotensive action, and respiratory activity remained constant.

Ramesh et al.[31] compared the efficacy of clonidine and diazepam (another benzodiazepine) in a prospective study for premedication in 50 children. Clonidine produced a level of sedation comparable with that of diazepam (0.2 $mg/kg^{-1}$), and the authors found a significant, favorable response to hemodynamic intubation with clonidine (3 $\mu g/kg^{-1}$) and no hypotension or bradycardia in their patients.

Experience with clonidine as a premedication for operations under local anesthesia is derived mainly from dentistry[32,33] and elective ophthalmic surgery. Weindler et al.[34] reported a prospective double-blind study on 44 patients with clonidine versus placebo as the premedication for retrobulbar anesthesia and showed a significant beneficial effect of clonidine with respect to preoperative anxiety, blood pressure, and intraocular pressure. Similar results were reported by Filos et al.,[35] who compared clonidine 3 $\mu g/kg^{-1}$ with 1.5 $\mu g/kg^{-1}$ and placebo in 60 elderly patients and found the latter dose to be as effective as the former but without lowering blood pressure and heart rate.

In our study of 150 patients, the five groups were too small to permit statistically significant differences in all comparisons. Nevertheless, the statistical trend confirms the beneficial effect of clonidine reported by many other authors. The most disadvantageous effects of midazolam are the lack of pain control and the reduced respiratory system activity caused by sedation. The most disadvantageous effects of morphine are respiratory depression, nausea, emesis, and hypertensive hematomas, which have led to its discontinuation as a premedica-

TABLE IV

Summary of Advantages and Disadvantages in Each Group*

| Properties | Midazolam | Morphine | Clonidine | Placebo | Control |
|---|---|---|---|---|---|
| Anxiety reduction | +++ | – | +++ | + | – |
| Pain control | – | +++ | +++ | + | – |
| Hemodynamic stability | ++ | ++ | +++ | – | – |
| Respiratory stability | + | – | +++ | +++ | +++ |
| Nausea | + | +++ | – | – | – |
| Emesis | – | +++ | – | – | – |

* +++, much; ++, mediocre; +, little; –, no effect.

tion in many institutions. The most important limitation of clonidine is the timing of its administration, which should be 60 to 90 minutes before surgery. Cunningham et al.[20] tried to shorten the latency period of clonidine with sublingual administration in an open-label study with 20 volunteers, but both routes of administration resulted in similar pharmacokinetic and pharmacodynamic effects.

Other authors[36–39] have reported their experience with other forms of clonidine application, including rectal, transdermal, or topical application. Epstein et al.[38] found a 57-percent reduction in pain in seven patients with neuralgia involving the oral cavity after the administration of clonidine (0.2 $mg/g^{-1}$) in a cream base. Rockemann et al.[40] applied clonidine epidurally for postoperative pain management and found a rapid and intense onset of analgesia in a study of 20 patients.

Sümpelmann et al.[41] successfully used clonidine in a prospective, randomized study for postoperative pain control to prevent morphine-related respiratory depression and nausea and emesis in patients having surgery in the maxillofacial region, in which vomiting is especially disadvantageous. In the current study, the advantages and disadvantages of the premedications for the five groups are shown in Table IV.

Our goal of decreasing anxiety, relieving pain, and stabilizing hemodynamic parameters with premedication was best achieved with clonidine. These properties particularly recommend clonidine as an adjunct to procedures performed on the face under local anesthesia.

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